Assessing PET parameters in oncologic ¹⁸F-FDG studies

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ABSTRACT

Positron emission tomography (PET) imaging, particularly oncologic applications of fluorine-18 fluorodeoxyglucose (¹⁸F-FDG), has become a routine diagnostic study. To better describe the malignancies, various PET parameters are used. In ¹⁸F-FDG PET studies, maximum standardized uptake value (SUV_{max}) is the most commonly used parameter to provide a measurement of the metabolic activity of the tumor. In obese patients, SUV corrected by lean body mass (LBM) (SUL or SUV_{SUL}) and in pediatric cases, SUV corrected by body surface area are recommended. Metabolically active tumor volume (MTV) is an important parameter to determine the local and total tumor burden. Total lesion glycolysis (TLG) (SUV_{mean} x MTV) provides information about average total tumor glycolysis. Some treatment response assessment protocols recommend using peak SUV (SUV_{peak}) or peak SUL (SUL_{peak}) of the tumor. Tumor to liver ratio (TLR) and tumor to blood pool ratio (SUR) is helpful when comparing studies for treatment response assessment. Dual-time point PET imaging with retention index (RI) can help differentiating malignant from benign lesions and may help detecting small lesions. Dynamic ¹⁸F-FDG PET imaging (dPET) and quantitative analysis can measure the metabolic, phosphorylation and de-phosphorylation rates of the lesions but they are mainly used for research purpose. In this article we will review the currently available PET parameters in ¹⁸F-FDG studies with their importance, usage, limitations, and reasons causing erroneous results.

Key words: PET, parameter, ¹⁸F-FDG, oncology, SUV

INTRODUCTION

Positron emission tomography (PET imaging) is based on detecting two simultaneously released 511 keV photons after positron (emitted from the injected radiotracer in the body) moves in the tissue for a distance (positron range), until it reaches rest mass, and then collides with a tissue electron causing annhilation reaction. PET imaging is a product of high technology but still have certain limitations related to various factors such as non-collinearity of 511 keV photons, positron range and parallax error which effect its sensitivity and spatial resolution in detecting small lesions (*1-3*). Non-collinearity causes less problem in small-animal PET scanners and therefore small-animal PET scanners have higher spatial resolution than standard human PET scanners (approximately 1 mm versus 4-6 mm) (*4*). Perhaps building small bore pediatric PET cameras may provide better imaging results than large bore standard PET cameras in detecting small lesions in pediatric population.

PET imaging, particularly with fluorine-18 fluorodeoxyglucose (¹⁸F-FDG), has been used commonly since the introduction of PET/computed tomography (CT) fusion cameras in early 2000s. PET images are visually assessed and also supported by quantitative parameters. Currently, the most commonly used PET parameter is standardized uptake value (SUV) in oncologic ¹⁸F-FDG studies. The other parameters include SUV normalized by lean body mass (SUL or SUV_{SUL}), metabolic tumor volume (MTV), total lesion glycolysis (TLG), tumor to liver and tumor to blood pool ratios, retention index in dual time-point PET studies and dynamic PET imaging parameters. Various other parameters are available with various radiotracers in oncologic, neurologic and cardiac PET studies which will not be discussed in this review article. However, most of the PET parameters described in this article can also be used in other oncologic PET studies with different SUVs in normal tissues and thresholds in differentiating malignant from benign lesions.

Standardized uptake value (SUV)

SUV is a commonly used PET parameter to measure the uptake of various radiopharmaceuticals, mainly ¹⁸F-FDG, in normal tissues and lesions (*5-7*). SUV is simply the ratio of activity concentration in the target tissue/lesion to activity concentration in the whole body.

SUV = KBq/ml (lesion or target tissue) / (decay corrected-injected activity (MBq)/patient weight (kg))

In above equation it is assumed that injected activity is uniformly distributed in the whole body and 1 ml of tissue weighs 1 gm (δ). Activity in the lesion or target tissue is decay corrected.

Due to metabolic heterogeneity or irregular borders of the tumor, maximum SUV (SUV_{max}) is used instead mean SUV (SUV_{mean}). SUV_{max} is the maximum voxel value of SUV in the tumor. SUV_{max} does not represent the whole tumor metabolic burden and is sensitive to image noise (9).

SUV generally accurately estimates the degree of uptake of radiopharmaceuticals in the lesions and normal tissues but is affected by various patient/biological and technical factors which can cause over- or underestimation of the activity in lesions and tissues. Suboptimal patient preparation, high blood glucose and insulin levels, diabetic status of the patient, body mass index/amount of body fat, age, gender, significant extravasation of activity, image acquisition and reconstruction parameters, conditions in post-injection uptake period, inaccurately entering patient data in the computer in regard to patient's weight, height, and injected activity, clock synchronization errors, inaccuracy in timing information in regard to injection time and imaging start time, effect of CT contrast material on attenuation corrected PET images, patient and organ motions, other diseases and medications effecting ¹⁸F-FDG uptake, etc. (Figures 1-3) (*8, 10-15*).

In the normalization of SUV, usually patient's total weight is used. However, in obese people, SUV is overestimated in the lesions and normal tissues (figure 1) (16, 17)). This is because ¹⁸F-FDG is mainly distributed in non-fat tissues and percentage of adipose tissue is high in obese people with minimal ¹⁸F-FDG accumulation in the fat. SUV normalized by lean body mass (LBM) (SUL or SUV_{LBM}), instead total weight, is recommended in obese patients (16,17). SUL also provides better comparison of PET images of a patient who has significant weight difference at the time of obtaining PET studies. Weight changes, particularly loss, are common in oncologic patients due to treatments or disease progression. SUV will be overestimated when the patient is overweight or obese, and underestimated when the patient is underweight or has cachexia as compared to SUV when the patient has normal body mass index (BMI). There are various ways of measuring LBM. LBM can be calculated through predictive equations using height and body weight (18). However, semi-direct measurements of LBM such as bioelectrical impedance analysis, dual-energy X-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI) can provide more accurate results (19). Using a more accurate method to measure LBM will provide more accurate SUL. However, all these methods have certain limitations, advantages and disadvantages. CT and MRI are the most precise and accurate methods but they are costly and complex to operate (19). Bioelectrical impedance analysis, and DXA are more accessible, easier to use and less costly (19). CT is not recommended in pregnant women and children due to radiation exposure. MRI is not suitable for the patients with metallic parts. A standard method for calculating LBM will allow more accurate comparison of PET studies of different institutes. SUL can be measured either directly by simply entering patient's LBM instead total weight in the PET computer or indirectly calculating it from SUV with the following formula:

 $SUL = (SUV \times LBM) / total weight$

In heavy patients, SUVs of blood, liver and spleen were up to twice those of lighter patients (*16*). In our recent study, SUVs of the liver and blood pool were significantly higher in obese patients as compared to patients with normal BMI and SUL_{mean} was approximately 75% of SU-V_{mean} in patients with normal BMI and 55% of SUV_{mean} in obese patients (*20*). For comparison, percentage of fat is 20-25 % of total body weight in young females with normal BMI, and 38-40 % in young obese females (*21*). If SUL is going to be used routinely, standard values (threshold value in differentiating benign from malignant lesions, and normal liver and blood pool values) should be determined. In our recent study, SUL_{mean} in the liver and blood pool were 2.2 and 1.8, respectively, in patients with normal BMI and were similiar in obese patients (*20*). SUL is not affected by body weight and amount of lean body mass (*20*).

Studies assessing SUV in children found that pediatric SUVs in the liver and tumor is lower than that of adults (22,23). SULs were also lower than normal adult values in children (23). These studies recommended using body surface area based calculation of SUV (SUV_{BSA}) in pediatric patients (22,23). Lower SUV and SUL in pediatric patients as compared to adults could be due to higher amount of brown fat in children which could competitively reduce the uptake of activity in other normal tissues and lesions.

There is minimal ¹⁸F-FDG uptake in white fat but brown fat shows moderate to high ¹⁸F-FDG uptake (*24, 25*). Brown fat is a tissue which produces heat to regulate body temperature. If there is severe brown fat uptake in a significant amount of area this may cause competitive reduction in ¹⁸F-FDG uptake in tumor causing visually low uptake and quantitatively low SUV. Brown fat is usually seen in greater amounts in pediatric population and some adults also show brown fat activity, particularly underweight people in cold temperature. Rarely is brown fat seen in overweight and obese patients and in such cases SUL may not be accurate if there is significant distribution of activity in brown fat.

Hyperglycemia is well known to reduce ¹⁸F-FDG uptake in the tumor and brain (figure 3). Brain ¹⁸F-FDG uptake and SUV gradually reduces with increasing blood glucose which is approximately 20% less than normal in low hyperglycemia (111-120 mg/dl) and 65% less than normal in significant hyperglycemia (>200mg/dl) (*12*). Brain and tumors both show high expression of GLUT1 and GLUT3 expression. Hyperglycemia reduces ¹⁸F-FDG uptake/SUV in the tumor which may be similar to above reductions in the brain. Measured tumor SUVmax can be multiplied by reduction factor of 1.25, 1.5, 2, 2.5 and 2.8 for the blood glucose ranges of 111-120, 121-140, 141-160, 161-200 and \geq 201 mg/dl, respectively, to correct SUV in hyperglycemic adults (*12*). Including the brain in whole body images can provide better idea on the effect of hyperglycemia with ¹⁸F-FDG uptake and SUV (figure 3) (*12*).

Metabolic tumor volume (MTV) and Total lesion glycolysis (TLG)

MTV is an important parameter which measures the metabolically active tumor volume (local and total tumor burden). Tumor tissue may contain necrotic or dead tissues or atelectasis and therefore the volume of the tumor may look larger on CT than that on PET. PET shows uptake in the metabolically active parts of the tumor and lack of uptake in dead tissues, necrosis and atelectasis but in inflammation. There are various methods (threshold-based and algorhythmbased) to measure MTV via computer programs (9, 26). Fixed absolute threshold methods may be more suitable to assess prognostic value of MTV and algorithm based methods seem to be better than fixed threshold methods for tumor response prediction or accurate tumor delineation for radiotherapy applications (9). If a computer program is not available to measure MTV, gross manual

measurement in each slice can be made which is time consuming. TLG is obtained by multiplying SUV_{mean} by MTV (27). SUV_{mean} is obtained by placing a region of interest (ROI) around the hottest part of the tumor.

MTV and TLG have prognostic value in a variety of malignancies and high MTV and TLG predicts a worsening prognosis (28-30). MTV and TLG are reported to correlate better with histopathological response compared to SUV_{max} (31). SUV_{max} is a single value reflecting only the highest pixel activity, however, TLG reflects two parameters: average whole tumor metabolic activity and volume of the tumor. MTV and TLG are also important when adjusting the dose of treatments. If there is metabolic heterogeneity in the tumor, TLG may be overestimated as the SUV_{mean} is obtained placing an ROI to the hottest part of the tumor. Moreover, accurate TLG can be calculated by measuring total lesion counts/activity and multiplying it by MTV. MTV and TLG appear to be useful parameters, but have not been commonly used in routine clinical practice.

Uptake ratio

Tumor to reference region activity ratio is another PET parameter. Most commonly used reference regions are liver and blood pool (32-35). Tumor SUV_{max} to liver SUV_{mean} ratio (TLR) and tumor SUV_{max} to blood pool SUV_{mean} ratio (SUR) are generally used. In liver and blood pool, SUV_{mean} provides more accurate results than SUV_{max}. Peak SUV (SUV_{peak}) of the tumor can also be used (36). SUV_{peak} is the average value within a small, fixed-size region of interest (ROI) in the hottest part of the tumor. PET response evaluation criteria in solid tumors (PERCIST) recommends using SUL_{peak} from the tumor when comparing two studies (37, 38). Tumor to liver and tumor to blood pool ratios are usually used to compare two PET studies for treatment response assessment (35, 37-39). In treatment response assessment of lymphomas, Deauville 5 point scale is recommended (1: no uptake in the tumor, 2: Tumor uptake is equal or less than mediastinum, 3: Tumor

uptake is greater than mediastinum but equal or less than liver, 4: tumor uptake is greater than liver, moderately increased and 5: tumor uptake is greater than liver, markedly increased) (*35*, *39*).

Uptake ratios may provide a better understanding of the metabolic activity of the tumor than a numerical value (SUV). For example, describing the metabolic activity of the tumor as three times of metabolic activity of the normal liver may give better idea than providing a numerical value (tumor SUV: 9). These parameters are also not affected by the patient weight, and injected activity. Tumor to blood pool ratio may be preferred over tumor to liver ratio as treatments and diseases may effect metabolic activity of the liver. On the other hand, reduced renal function can cause increased blood pool activity which may reduce the accuracy of tumor to blood pool ratio.

High blood glucose generally reduces tumor ¹⁸F-FDG uptake but there are various reports on its effect on liver and blood pool activity. Per our recent assessment, hyperglycemia does not affect liver and blood pool activity (*12, 40, 41*). However various other studies and a recent metaanalysis study reported that hyperglycemia increases liver and blood pool activity (*42-46*). Thus, in hyperglycemic patients, tumor to liver or tumor to blood pool activity ratio should be used carefully.

Dual-time point PET imaging and retention index

Dual-time point PET imaging (obtaining both early-standard and delayed PET images) have been used extensively in various cancers to differentiate benign from malignant lesions. In addition to visual assessment, retention index (RI, percent SUV difference in early and delayed images) are calculated in these studies as seen below.

$$RI(\%) = 100 x ((SUV_{max} delayed - SUV_{max} early) / SUV_{max} early)$$

Dual-time-point PET imaging improved the diagnostic accuracy for malignant lung nodules (47). However, in lung lesions with size and SUV_{max} are greater than 10 mm and 2.5, respectively, authors did not recommended dual-time-point 18F-FDG-PET imaging to differentiate between malignant and benign pulmonary lesions (48). Tian et al. found a significant differences in the RI between the malignant and benign bone lesions, which was approximately 18 versus 7, respectively (49). In breast, dual time point imaging improved PET/CT accuracy in patients with a suspected breast malignancy over single-time-point imaging demonstrating increasing ¹⁸F-FDG uptake over time in breast tumors and decreasing uptake in benign lesions (50). In grading brain tumors, SUV_{max} and SUV_{peak} from the delayed image were more efficient than those of early images (51). Delayed imaging may also allow better detection of small lesions due to improved contrast between the lesion and the background (52).

Dynamic PET imaging

Dynamic PET (dPET) imaging with ¹⁸F-FDG and quantification approaches helps to estimate the rates of glucose transport, phosphorylation and dephosphorylation in the tumor (*53*, *54*). Compartment modelling is used to analyze the dynamic imaging data. A two-tissue compartment model was first described by Sokoloff et al. (*55*). Tracer flows between the blood compartment and tissue compartments. Four transport rates (k1, k2, k3, k4) describe the exchange of the tracer between blood and tissue compartments (*54*). In ¹⁸F-FDG studies, k1 reflects the influx, k2 the efflux, k3 the phosphorylation rate and k4 the dephosphorylation rate of the glucose analogue (*54*). Patlak graphical analysis is an approach for the calculation of the metabolic rate of glucose (*56*). The metabolic rate of ¹⁸F-FDG (MRFDG) can then be calculated using the formula [MRFDG = Ki x (plasma glucose/lumped constant)] (*54*). The lumped constant is the ratio of ¹⁸F-FDG uptake to glucose uptake and is not exactly known for the tumors (*54*). Influx rate can be calculated using the rate constants of the two-tissue compartment and the formula $[Ki = (k1 \times k3/k2 + k3)]$ (54). dPET with quantification is time consuming and requires dedicated evaluation software and expertise and is usually applied in research. When a software is not available to measure dPET parameters, ¹⁸F-FDG uptake rate can be grossly assessed by obtaining dynamic images over the tumor (e.g. 1 min, 60 frames) after the injection of ¹⁸F-FDG and generating a time activity curve by placing a same size ROI in the same slice of the tumor in all frames and applying decay correction.

¹⁸F-FDG dPET imaging have been studied in various malignancies in differentiating malignant from benign lesions and grading malignant tumors (*57-59*). In a study of soft tissue sarcomas, SUV, k1, Ki and fractal dimension were higher in sarcomas than benign tumors and SUV, vascular fraction, k3, Ki, and fractal dimension were higher in recurrent lesions than in scar tissues (*59*). In another study, k3, Ki and MRFDG were significantly higher in higher grade tumors, progesterone-receptor negative and highly-proliferating tumors as well as in triple-negative and hormone-receptor negative/HER2-positive subtypes (*53*). It also appears that ki was significantly higher in node-positive than in node negative disease (*53*).

CONCLUSION

Various PET parameters are available for ¹⁸F-FDG studies and we summarized them in this article with their importance, usage, limitations, and reasons causing erroneous results.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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FIGURE LEGENDS

Figure 1. Effect of body weight on SUV. Whole body ¹⁸F-FDG PET maximum intensity projection image of an obese patient (59 year-old female, weight: 114 kg, height:165 cm, lean body mass: 59.4 kg). SUV_{mean} in the liver and blood pool are 5 and 4.1, respectively, which are above normal values and higher than visually seen activity in the liver and blood pool. SUV corrected by lean body mass (SUL) is 2.6 in the liver and 2.1 in the blood pool. Overweight/obesity can cause overestimation of SUV also in the lesions/tumor.



Figure 2. ¹⁸F-FDG PET whole body maximum intensity projection image and transaxial selected PET slice from the liver in an adult patient with erroneously low SUV (Liver SUV_{mean}:0.4). Inaccurate entrance of amount of injected ¹⁸F-FDG activity in the PET computer (3000 MBq instead of 300 MBq) caused significantly low SUV in the liver and other tissues in this patşent. When measured SUV is not matching with visual findings, it is important to check the patient data in the PET computer (weight, height and injected dose). In addition, as the activitity is decay corrected for SUV, the accuracy of injection and imaging start times should also be checked. Clocks used in the department should be synchronized.



Min: 0.4 SUV Max: 0.5 SUV Mean: 0.4 SUV StdDev: 0.04 SUV **Figure 3.** Effect of high blood glucose on brain ¹⁸F-FDG uptake. ¹⁸F-FDG PET whole body maximum intensity projection images. A-48 year-old female with recently diagnosed breast cancer. Fasting blood glucose: 97.2 mg/dl. SUV_{max} in right frontal cortex: 19.6. SUV_{mean} in liver: 3.6, SUV_{mean} in blood pool: 3.2. B-52 year-old male with a pancreatic lesion. Fasting blood glucose: 216 mg/dl. SUV_{max} in right frontal cortex: 5, SUV_{mean} in liver: 2.7, SUV_{mean} in blood pool: 1.5. Visually there is diffusely decreased uptake in the brain. Patient does not have cranial symptoms. Compare the brain activity with the liver uptake and bladder activity in both cases.



Normal blood glucose

High blood glucose